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10/717,653	11/21/2003	Thomas P. Jerussi	4821-529-999	9144

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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	PAPER NUMBER
1611	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,653	JERUSSI, THOMAS P.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 05/30/08, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Status of the Claims

Claims 41-51 are currently pending in this application and are the subject of the Office action.

Response to applicant's arguments/remarks

Rejection under 103(a)

Applicant contends that this rejection should be withdrawn (see applicant's Response, received 05/30/08, at pages 4-7):

1) Contrary to the examiners allegation that the claims are obvious because a clear definition is lacking for the term "enantiomerically pure (S)-didesmethylsibutramine," and that racemic didesmethylsibutramine may be encompassed by this term is without merit because the term is clearly defined in the specification so as to exclude the racemic didesmethylsibutramine.

2) The examiner failed to address applicant's arguments set forth in applicant's previous response.

3) The cited references fail to establish that there would have been a reasonable expectation that (S) –didesmethylsibutramine would have "better"

pharmaceutical properties than racemic didesmethylsibutramine or racemic sibutramine (see specification, page 5).

4) Harrison's does not provide any basis to conclude that any and all antidepressants are effective in treating narcolepsy. Harrison discloses that compounds including viloxzine hydrochloride and fluoxetine are under evaluation for narcolepsy, which clearly implies that each and every antidepressant must be separately evaluated for their efficacy and/or safety for the treatment of narcolepsy. Harrison disclosure supports an "obvious to try" standard, which is improper.

5) A copy of the BPAI decision in Ex parte Young is submitted as Exhibit A, wherein the Court found that no reasonable expectation of success in arriving at appellants claimed method of treatment using a single enantiomer of a pharmaceutical which was previously discloses in racemic form (BPAI Appeal No. 2004-1592).

6) A person skilled in the art would have no basis to "predict with a reasonable expectation of success whether one enantiomer of the claimed compound would have better pharmaceutical properties than the racemate itself.

In response, the rejection is withdrawn.

Lack of written description rejection under 112, 1st

This rejection is rendered moot by the claim amendment deleting the term "solvate."

NEW REJECTION

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41-51 are rejected under 103(a) as being unpatentable over Scott et al. (Scott et al. The effects of BTS 54 505, a metabolite of sibutramine, on monoamine and excitatory amino acid-evoked responses in the dosolateral geniculate nucleus in vivo. Br. J. Pharmacol., 111:97-102 (1994), in view of Young (WO 94/00114) and Adda et al. (Adda et al. Narcolepsy and depression. Arq. Neuropsiquiatr. 1997;55(3A):423-6, abstract only).

Claim 41 recites [a] method of treating narcolepsy comprising administering to a patient a therapeutically effective amount of enantiomerically pure (S)-didesmethylsibutramine, or a pharmaceutically acceptable salt thereof." Claim 42 recites "wherein the (S)-didesmethylsibutramine comprises greater than about 80 percent by weight of didesmethylsibutramine." Claim 43 recites "wherein the (S)-didesmethylsibutramine comprises greater than about 90 percent by weight of didesmethylsibutramine." Claim 44 recites "wherein the (S)-didesmethylsibutramine comprises greater than 95 percent by weight of didesmethylsibutramine."Claim 45 recites "wherein the amount of (S)-didesmethylsibutramine administered is from about 0.1 mg to about 60 mg per day."Claim 46 recites "wherein the amount of (S)-didesmethylsibutramine administered is from about 2 mg to about 30 mg per day." Claim 47 recites "wherein the amount of (S)-didesmethylsibutramine administered is from about 5 mg to about 15 mg per day." Claim 48 recites "wherein the (S)-didesmethylsibutramine is administered orally, mucosatly, rectally, transdermally, topically or parenterally." Claim 49 recites "wherein the (S)-didesmethylsibutramine is administered orally." Claim 50 recites "wherein the (S)-

didesmethylsibutramine is administered parenterally." Claim 51 recites "wherein the (S)- didesmethylsibutramine is administered intravenously, intramuscularly or subcutaneously."

Scott et al. (Scott et al. The effects of BTS 54 505, a metabolite of sibutramine, on monoamine and excitatory amino acid-evoked responses in the dosolateral geniculate nucleus in vivo. Br. J. Pharmacol., 111:97-102 (1994)) is added to show the general knowledge regarding didesmethylsibutramine. Scott et al. teach that the primary and secondary amine metabolites of sibutramine (i.e. BTS 54 505, or desmethylsibutramine, and BTS 54 3554, or didesmethylsibutramine) have a similar pharmacological profile to the parent compound (= sibutramine) in vivo, but are up to 100 fold more potent than sibutramine as monoamine uptake inhibitors in vitro (page 97, column 1, lines 11-16; see also Figure 1. Scott et al. teach that the in vitro data indicate that the pharmacological effects of subitramine in vivo are mainly due to the activity of its primary and secondary amine metabolites (page 97, column 1, lines 16-20). Scott et al. also disclose that tricyclic antidepressants have a number of side effects which arise from their affinity for muscarinic cholinoceptors and histamine receptors; these side effects may limit their therapeutic use in the treatment and/or prevention of NMDA-induced toxicity and neurodegeneration (page 101, column 2, last paragraph, lines 15-21). Scott et al. further disclose that since sibutramine and its active metabolite BTS 54 505 (= didesmethylsibutramine) have no significant affinity for muscarinic receptors, α1, α2, β adrenoceptors, dopamine D1 and D2 receptors, and 5-HT1 and 5-HT receptors, sibutramine and

BTS 54 505 may result in fewer and less pronounced side-effects than the tricyclic antidepressants (page 101, column 2, last paragraph, lines 21-27). However, Scott et al. do not teach narcolepsy or pure (-) didesmethylsibutramine.

Young is added to show the general knowledge regarding the parent compound sibutramine (e.g. dosing, route of administraton) and its optically pure enantiomers and methods for preparing the same. Young discloses a method of using racemic sibutramine and optically pure (-) sibutramine for treating Parkinson's disease. Young teaches optically pure and substantially optically pure (-) sibutramine and methods of obtaining optically purified stereosiomers of sibutramine (page 4, lines 1-10; and page 17, line 34 to 32). Young teaches that optically pure (-) sibutramine possesses potent activity in treating disorders ameliorated by inhibition of neuronal monoamine reuptake (e.g. Parkinson's disease and depression) while avoiding the adverse effects associated with the administration of the racemic mixture of sibutramine (page 2, lines 2-4; page 10, lines 8-32). Young discloses that optically purified stereoisomers of sibutramine are most readily obtained by resolving the racemic mixture of sibutramine by fractional crystallization of the diastereomeric salts formed with optically active resolving agents via a commonly used conventional process (page 17, line 34 to page 18, line 32). Young teaches that in general the recommended dose range of sibutramine is from about 1 mg to about 60 mg per day, which overlaps with the instant claimed dosage range for optically pure (-) diesmethylsibutramine (page 19, line 5-9). Young teaches an antidepressant composition for the treatment of a human in need of antidepressant therapy which comprises an

amount of (-) sibutramine, substantially free of its (+) sterioisomer, wherein said of (-) sibutramine is in an amount sufficient to alleviate depression. (page 11, line 28 to page 12, line 3). Young also teaches that any suitable route of administration may be employed for providing the patient with an effective dosage of (-) sibutramine e.g. oral, rectal, parenteral, transdermal; dosage forms include tablets, troches, dispersions, suspsensions, solutions, capsules, patches, and the like (page 21, lines 7-14). Young does not teach optically pure (-) didesmethylsibutramine or narcolepsy.

Adda et al. (Adda et al. Narcolepsy and depression. Arq. Neuropsiquiatr. 1997;55(3A):423-6, abstract only) teach that the main symptoms of narcolepsy include excessive daytime sleepiness and cataplexy and that depressive complaints are occasionally reported (abstract).

It would have be obvious to a person of skill in the art at the time the instant invention was made to use the optically pure (S) form of BTS 54 505 (= didesmethylsibutramine) as taught by Scott et al. to treat narcolepsy as taught by Adda et al. to control symptoms of depression. One would have been motivated to treat narcolepsy with optically pure (S) BTS 54 3554 because Scott et al. teach that BTS 54 3554 (didesmethylsibutramine) has a similar pharmacological profile to the parent sibutramine compound in vivo (e.g. treating depression; page 97, column 1, lines 11-16; see also Figure 1) and that sterochemical purity is of importance in the field of pharmaceuticals since certain isomers may actually be deleterious and not simply inert (page 3, lines 23-31). One would have expected to successfully separate the (S)-didesmethylisubutramine from the (R) isomer for

use to treat narcolepsy because Young teaches a well known crystallization fractionation method for separating optical isomers such as subitramine and a major portion of the chemical structure of sibutramine is identical to the chemical structure of didesmethylsibutramine (Cf. In re Kerhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980). In addition, Adda et al. teach that depression is observed in patients with narcolepsy. To the extent that (-)-didesmethylsibutramine has a similar pharmacological profile to the parent sibutramine compound, which is known to effective in treating depression, a person of skill in the art at the time the invention was made would have similarly expected to successfully use (-)-didesmethylsibutramine to treat the symptoms of depression, including the symptoms of depression associated with narcolepsy.

Thus, a person of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonably predictability.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

11 September 2008

/C. R./ Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611